REMARKS

Amendments to the specification. The specification has been amended to add "SEQ ID NO:" identifiers that correspond to the sequence listing filed September 14, 2006. No new matter has been added by way of these amendments.

Amendments to the claims. Prior to entry of this paper, claims 1, 15, 16, 32-36 and 38 were pending, claims 1, 32-34 and 38 were withdrawn, and claims 15, 16, 35 and 36 were rejected.

In this paper, claims 35 and 36 have been amended and claims 40 and 41 have been added. The term "CYP2S1" in claims 35 and 36 have been expanded with the full name of "cytochrome P450 2S1" as disclosed in the abstract of the application. Support for amended claim 35 can be found in, *e.g.*, the section of the specification entitled "Testing Drug effectiveness and/or toxicity" on pages 7-8 and the "Methods" section on pages 10-11 of the specification as filed. Support for replacement of "an increase" with "a higher" in claim 36 can be found, *e.g.*, on page 14 of the specification in the paragraph entitled "3. Expression of CYP2S1 in lesional psoriatic skin."

New claims 40 and 41 are identical to pending claims 15 and 16 except that the new claims depend from claim 36. Support for these new claims can be found, *e.g.*, in original claims 15 and 16 and in the first paragraph of page 7 of the specification as filed. No new matter is added by way of this amendment.

Thus, with entry of this amendment, claims 15, 16, 35, 36, 40, and 41 are pending and at issue.

I. Drawings and Specification Formalities

The Examiner has objected to Figure 7 because it discloses a sequence without identifying it by SEQ ID NO in either the drawing itself or the Brief Description of Drawings. Applicants have amended the specification to add the term "SEQ ID NO:10" corresponding to the Sequence Listing filed September 14, 2006 to the description of Figure 7.

The Examiner has also objected to the specification because it does not identify the sequences referenced in the specification with the proper SEQ ID NO. Applicants have amended the specification to add the SEQ ID NO's corresponding to the Sequence Listing filed September 14, 2006 to locations in the specification referencing sequences.

II. Claim Objections

The Examiner has objected to claims 15-16 and 35-36 due to the recitation of "CYP2S1." The Examiner asserts that, unless the acronym is obvious or commonly used in the art, the claims must recite the full name at least once.

Applicants have amended independent claims 35 and 36 to comply with the Examiner's request by expanding the term "CYP2S1" to "cytochrome P450 2S1."

III. Claim Rejections – 35 U.S.C. § 112, second paragraph

Claims 15-16 and 35 have been rejected under 35 U.S.C. §112, second paragraph, as being indefinite because, according to the Examiner, claim 35 recites the phrase "the treated first sample" without sufficient antecedent basis.

Applicants have amended claim 35 to clarify that the "treated first sample" is a sample of the treated diseased skin, extracted from a location adjacent to the site of extraction of the untreated first sample of diseased skin in (a) of claim 35.

Claims 15-16 and 35 have been rejected under 35 U.S.C. §112, second paragraph, as being indefinite because, according to the Examiner, claim 35 recites the phrase "detecting effectiveness of a skin treatment," but is it unclear how to do so. According to the Examiner, "the CYP2S1 levels of the treated first sample [are] compared to another sample, whose basal CYP2S1 levels may be higher or lower than the basal CYP2S1 of the untreated first sample" (page 5 of the Office Action). The Examiner also asserts that the step of administering a skin treatment to the untreated first sample is missing.

Applicants have amended claim 35 by adding for clarification that the skin treatment is effective if CYP2S1 levels are modulated. Applicants have also amended claim 35 to recite that the samples for comparison are adjacent to each other (such that the basal levels of samples are presumed to be the same) and the skin treatment is administered to the diseased skin of the patient.

Claim 36 has been rejected under 35 U.S.C. §112, second paragraph, because, according to the Examiner, the phrase "increase in the CYP2S1 level" is unclear and the claimed method is lacking an essential step. The Examiner asserts that it is unclear how CYP2S1 can increase between the first and second sample since only basal levels of CYP2S1 in the first and second samples are detected.

Applicants have amended claim 36 to replace "an increase" with "a higher" to clarify that a higher level, not an increased level, of CYP2S1 is observed in the first sample compared to the second sample. In view of this amendment, Applicants do not believe that there is a step missing in claim 36. The preamble of claim 36 refers to chemicals which are already identified as being metabolisable by CYP2S1. As recited in the body of the claim, if a subject is observed to have an increased level of CYP2S1 in diseased skin in comparison to normal skin, such a chemical treatment may find utility in treating the skin condition because it would be expected that the chemical agent would be preferentially metabolized by the diseased skin of the subject.

In view of the above amendments and remarks, Applicants respectfully request withdrawal of the 35 U.S.C. § 112, second paragraph, rejections.

IV. Claim Rejections – 35 U.S.C. § 112, first paragraph – Written Description

Claims 15-16 and 35-36 have been rejected under 35 U.S.C. 112, first paragraph, for lack of written description. The Examiner asserts that the specification does not supply sufficient support for the genus of skin treatments as recited in the claims because the examples provide only two examples of skin treatments (*i.e.*, coal tar and all-trans retinoic acid) and the specification does

not provide a relationship between the structure of the skin treatments and an increase or decrease in CYP2S1 levels.

Applicants respectfully traverse the written description rejection. The present invention teaches for the first time that existing therapeutic treatments used on diseased skin may be metabolized by CYP2S1 and that a patient's CYP2S1 "status" may be a determining factor as to whether or not such treatments may be effective or otherwise in an individual. New treatments *per se* are not being claimed, but rather the invention provides a method of determining whether a therapeutic regime may be useful in a particular subject, resulting in possible improved therapeutic outcomes for a subject. There is, therefore, no limitation whatsoever in terms of the skin treatments which could be tested. Any type of drug, in whatever form, can be tested as recited in claim 35, but only those which serve to elicit a response which is different in terms of CYP2S1 levels compared to untreated diseased skin would be considered as a possible effective treatment. Any chemical which is metabolized by CYP2S1 can be considered a favorable skin treatment as set forth in claim 36.

Applicants further point out that possible skin treatments are described in detail in the specification on pages 5-6 and include antisense oligonucleotides, RNAi molecules, chemical drug candidates, peptides, proteins, a combination of radiation and chemicals, and antibody products. Moreover, the Examiner is requiring the specification to provide a relationship between the structure of the skin treatments and an increase or decrease in CYP2S1 levels, however knowing this type of relationship is not required for practicing the claims. To the contrary, the claims recite methods for determining this relationship. Claim 35 recites a method for determining whether a skin treatment increases or decreases CYP2S1 levels and is therefore effective. Claim 36 sets forth comparing two untreated samples to determine whether a skin treatment may be effective.

For at least these reasons, Applicants respectfully request withdrawal of the written description rejection.

V. Claim Rejections – 35 U.S.C. § 112, first paragraph – Enablement

Claims 15-16 and 35-36 have been rejected under 35 U.S.C. §112, first paragraph, for lack of enablement. The Examiner asserts that, while the specification enables methods of detecting the effectiveness of a skin treatment or whether a subject is likely to respond to a skin treatment by administering coal tar or all-trans retinoic acid, the specification does not enable such methods when administering any skin treatment. According to the Examiner, the specification does not provide sufficient guidance to know whether a compound, with the exception of coal tar and all-trans retinoic acid, will increase or decrease CYP2S1 levels.

As discussed by the Examiner, the Wands factors include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breath of the claims. Addressing (4) the nature of the invention and (8) the breath of the claims, new treatments *per se* are not claimed, but rather the claimed invention provides assays for determining whether a treatment can modulate CYP2S1 levels and be effective and assays for determining whether a treatment can be effective based on different expression levels of CYP2S1 in normal and diseased skin.

(2) The amount of direction or guidance and (3) the presence or absence of working examples are sufficient to practice the claimed invention. The specification discloses several ways to detect the levels of CYP2S1 in skin as recited in the claims, such as PCR and immunohistochemical analysis (*see* pages 11-13) and as described in the section entitled "Methods" (*see* pages 6-7). The present invention clearly teaches that CYP2S1 is associated/responsible for metabolism of topically administered drugs (*see*, *e.g.*, page 16) and shows that diseased patients with differential CYP2S1 expression respond favorably or otherwise due to their CYP2S1 status (*see*, *e.g.*, summarized in the first complete paragraph on page 19). Thus, it is quite clear to the skilled addressee that any compound could be tested in the manner taught by the claims. The

specification is not intended to provide "guidance as to which of the essentially infinite possible choices is likely to be successful" (*see* page 10 of the Office Action), as that is exactly what the methods as claimed are intended to ascertain.

Based on (5) the state of the prior art, (6) the relative skill of those in the art, and (7) the predictability or unpredictability of the art, one of ordinary skill in the art could practice the claimed invention using the guidance supplied by the specification as discussed above. Merely routine experimentation is (1) the quantity of experimentation necessary to practice the claimed invention in light of the teachings of the specification, the prior art, and the knowledge of one of ordinary skill in the art. For at least these reasons, Applicants respectfully request withdrawal of the enablement rejection.

VI. Claim Rejections – 35 U.S.C. § 103

Claims 15-16 and 35-36 have been rejected under 35 U.S.C. 103(a) as being unpatentable over Bickers (Bickers *et al.*, *J Clin Invest* 1978, 62:1061-1068) and Rylander (Rylander *et al.*, *Biochem Biophys Res Comm* 2001, 281:529-535). The Examiner assert that Bickers teaches a method for determining the effectiveness of coal tar as a skin treatment by measuring enzyme levels, but not including the levels of CYP2S1. Rylander teaches, according to the Examiner, the isolation and cloning of CYP2S1, methods of detecting CYP2S1 using an antibody, and methods of measuring CYP2S1 mRNA. The Examiner contends that it would have been obvious to one of ordinary skill in the art at the time of the invention to use the CYP2S1 of Rylander in the Bickers method, one would have been motivated to do so because CYP2S1 has been cloned to allow for easier and more specific detection of CYP2S1, and there would have been a reasonable expectation of success because Rylander teaches the sequence for CYP2S1 and how to detect CYP2S1.

Applicants respectfully traverse the rejection. Bickers merely teaches that one particular cytochrome P-450 dependent enzyme (AHH) is induced upon application of coal tar to the skin.

However, Bickers does not show that other cytochrome P-450 enzymes are induced in this manner as set forth in claim 35 and, moreover, there is no suggestion that there is any change in the level of enzymatic activity between "normal" and "diseased" skin as recited in claim 36. Of course as conceded by the Examiner, Bickers does not refer to the CYP2S1 enzyme, as this was not even identified until over 20 years later.

Rylander teaches the identification and tissue distribution of CYP2S1, but does not identify its expression in skin as required by the claims and certainly does not disclose the differential expression of CYP2S1 in terms of "normal" versus "diseased" skin as recited in claim 36.

In contrast, the present inventors were the first to identify that differential levels of CYP2S1 expression can be observed in "normal" and "diseased" skin as recited in claim 36 and moreover that this enzyme is induced in the skin by topical administration of drug agents, such as retinoids or coal tar, as set forth in claim 35. These observations led to novel and inventive applications, which simply could not have been predicted or postulated in view of the prior art cited by the Examiner.

Even if one were to combine the teachings of Bickers and Rylander, the furthest anyone could go with such teachings, would be that CYP2S1 may be expressed in the skin and may be responsible for some degree of metabolizing drug substances applied to the skin. Nevertheless, Rylander teaches CYP2S1 expression in many tissue types, but also shows that it is not expressed in all types of cells. Thus, it is quite conceivable that CYP2S1 would not be expressed in skin tissue. There is little motivation on the basis of these documents to identify whether CYP2S1 is expressed in skin tissue as required by the claims and no reasonable expectation that CYP2S1 would be expressed in the skin. Such an expectation is required for a finding of obviousness. *See* MPEP §2143.02. Moreover, neither of these documents recognize that aberrant/unusual CYP2S1

expression in diseased skin maybe an important determinant of individuality of response to topical drug treatment and photo(chemo) therapy.

For at least these reasons, Applicants respectfully request withdrawal of the obviousness rejection.

VII. Conclusion

In view of the above amendments and remarks, it is respectfully requested that the application be reconsidered, that the amendment be entered, and that all pending claims be allowed and the case passed to issue. If there are any other issues remaining which the Examiner believes could be resolved through a Supplemental Response or an Examiner's Amendment, the Examiner is respectfully requested to contact the undersigned.

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Respectfully submitted,

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